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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/254,288	04/02/1999	WOLFGANG TESCHNER	040433/0177	6758

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EXAMINER

SAUCIER, SANDRA E

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 12/18/2001

19

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/254,288

Applicant(s)

Teschner et al.

Examiner

Sandra Saucier

Art Unit

1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

1) ☒ Responsive to communication(s) filed on Sep 17, 2001

2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

## Disposition of Claims

4) ☒ Claim(s) 14-18, 20-31, 33, and 34 is/are pending in the application

4a) Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration

5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.

6) ☒ Claim(s) 14-18, 20-31, 33, and 34 is/are rejected.

7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.

8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirements.

## Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some\* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

18) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

19) ☐ Notice of Informal Patent Application (PTO-152)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_

20) ☐ Other: \_\_\_\_\_

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**DETAILED ACTION**

Claims 14-18, 20-31, 33, 34 are pending and are considered on the merits.

***Continued Prosecution Application***

The request filed on 9/17/2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/254288 is acceptable and a CPA has been established. An action on the CPA follows.

The request for suspension has terminated as of 10/17/2001, one month after the date the request for suspension of action was filed.

***Claim Rejections - 35 USC § 112***

**INDEFINITE**

Claims 14-18, 20-31, 33, 34 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Citrate is a dicarboxylate having 4 carbons. It is unclear how the exchange of citrate for a dicarboxylate which may be citrate (because the term "dicarboxylate" encompasses citrate) creates a medicament which does not take up metals as the preamble of claim 14 states. Claims 14 and 31 are, therefore, confusing. Citrate is a known chelating agent. The exchange of citrate for citrate which is encompassed by the claim, does not and cannot lead to a metal free product.

Claim 16 remains indefinite because it recites "using a salt of a carboxylic acid". This may be a mono-, di- or tri-acid. The term expands the independent claim which is limited to mono or dicarboxylic acids or salts thereof. A suggestion is to use the or said "monocarboxylate, dicarboxylate, monocarboxylic or dicarboxylic acid".

***Claim Rejections - 35 USC § 102***

Claims 14-17, 20-23, 26, 28, 31, 33, 34 remain rejected under 35 U.S.C. 102(e) as being clearly anticipated by US 5561115 [A].

The claims are directed to a process of producing a plasma protein containing product which is substantially free from undesired metals by

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exchanging the citrate, which is a chelating agent, in the product for another mono or dicarboxylic acid or salt thereof.

US 5561115 discloses a process of preparing an albumin solution comprising adding sodium caprylate to Cohn fractions II+III of plasma. As Cohn fractions are routinely produced from plasma derived from citrated blood, they are considered to contain at least some of the original citrate. The sodium caprylate is said to separate the colloidal solution into a supernatant phase and a disperse or colloidal phase (col. 3, l. 3). Please note that this is not a precipitating condition. A colloid is not a precipitate, and therefore by definition, the conditions are non-precipitating see Grant and Hackh's Dictionary, page 145. The addition of sodium caprylate while heating also inactivates viruses (col. 5, l. 3). The suspension is then further diafiltered with 0.02M sodium caprylate and treated by filtration to prepare a sterile albumin preparation (col. 3 and example I).

US 5561115 discloses albumin containing 7.53 ppb aluminum (col. 7, Results).

#### *Response to Arguments*

Applicant's arguments filed 12/4/00 have been fully considered but they are not persuasive.

Applicants argue that the process of '115 teaches the addition of caprylate to a colloidal effluent. The caprylate separates the colloidal solution into a (supernatant) phase containing the albumin and a disperse (colloidal) phase containing other proteins and debris. Please note that in column 3, lines 25-35, the reference has defined a partitioning agent (caprylate) as opposed to precipitating agent. Please note that the formation of a two phase colloid by addition of caprylate is not precipitation according to the definitions of '115. Thus, applicants' argument that their process is distinct because it is performed without precipitation, while '115 teaches a process that "amounts to precipitation" is unpersuasive. Applicants' might contemplate the insertion of specific process steps which are not taught in '115 to better distinguish their process from the prior art.

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Further, although a product is claimed by a product by process claim, the product itself must be shown to be distinct from the prior art product. This applicants have not done.

As stated in *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977):

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product...Whether the rejection is based on "inherency" under 35 USC § 102 , on "*prima facie* obviousness" under 35 USC § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidence by the PTO's inability to manufacture products or to obtain and compare prior art products.

Because the claimed and prior art products reasonably appear to be identical or substantially identical, or are produced by identical or substantially identical processes, the burden of persuasion is shifted to applicants "to prove that the prior art products do not necessarily or inherently possess the characteristics of [their] claimed product."

Claims 14-16, 18, 20-23, 28, 29, 31, 33, 34 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by US 5372997 [B].

US 5372997 discloses a process for removing aluminum from albumin comprising:

adding acetic acid (acetate) to the Cohn's fraction V, adding NaOH to the fraction, running the solution through an anion exchange column which has been washed with NaCl and equilibrated with NaAc. Because only the presence of NaCl is required in claim 29, it is considered to be reasonably expected that an exchange column which has been washed with NaCl will have at least some NaCl remaining on it, and this fulfills the claim limitation. Because the Cohn's process for fractionating plasma has a step of adding EtOH at a low temperature, which is known to inactivate viruses, a viral inactivation is considered to have been performed on the albumin prior to the exchange of

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citrate. A low aluminum product is produced and stored in low aluminum containing glass.

*Response to Arguments*

Applicants argue that the '997 patent does not disclose a) the presence of citrate in the starting material, b) use of water soluble mono or dicarboxylic acids or salts thereof as exchange partners for citrate.

a) Cohn's fraction V is derived from citrated blood, therefore, it is reasonable to assume that Cohn's fraction V as produced by the well known Cohn's fractionation process inherently retains citrate. Clear evidence that Cohn's fraction V does not contain citrate would advance prosecution. It is noted that the albumin discussed by applicants as being suitable for their process, (a protein blood product which contains citrate) is a product of the Cohn's fractionation method (page 6).

b) Please note that sodium acetate is a monocarboxylate. Thus, it would inherently displace citrate. An exchange, as the term is used in the specification, is an equilibrium process which would occur whenever citrate and acetate are both present with protein(s) such as a Cohn's fraction. Thus, applicants' arguments are unpersuasive. Insertion of specific steps of applicants' process which are distinct from the disclosures of the prior art might advance prosecution.

*Claim Rejections – 35 USC § 103*

Claims 14-18, 20-29, 31, 33 and 34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5561115 [A] or US 5372997 [B] and US 5118794 [C].

The claims are directed to a process for reducing the concentration of metals in citrated plasma or a citrated plasma product comprising: exchanging, particularly by filtration or a chromatographic method, the citrate anion for a mono- or di-carboxylic anion, particularly tartrate or caprylate anions, without precipitating the plasma proteins, recovering a plasma protein, carrying on. A product of the process is also claimed.

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Some of the claims require a virus inactivation step after removal of the citrate-bound metal.

The references are relied upon as explained below.

US 5561115 discloses a process of preparing an albumin solution comprising adding sodium caprylate to Cohn fractions of plasma. As Cohn fractions are routinely produced from plasma derived from citrated blood, they are considered to contain at least some of the original citrate. The sodium caprylate is said to separate the colloidal solution into a supernatant phase and a disperse or colloidal phase (col. 3, l. 3). Please note that this is not a precipitating condition. A colloid is not a precipitate, see Grant and Hackh's Dictionary, page 145. The suspension is then further diafiltered with 0.02M sodium caprylate and treated by filtration to prepare a sterile albumin preparation (col. 3 and example I). This gives a preparation with low aluminum and citrate content. This reference lacks the specific disclosure of a step for the inactivation of viruses performed after recovery of the processed albumin.

US 5372997 discloses a process for removing aluminum from albumin comprising adding acetic acid (acetate) to the Cohn's fraction V, adding NaOH to the fraction, running the solution through an anion exchange column which has been washed with NaCl and equilibrated with NaAc. Because only the presence of NaCl is required in claim 29, it is considered to be reasonably expected that an exchange column which has been washed with NaCl will have at least some NaCl remaining on it, and this fulfills the claim limitation. Because the Cohn's process for fractionating plasma has a step of adding EtOH at a low temperature, which is known to inactivate viruses, a viral inactivation is considered to have been performed on the albumin prior to the exchange of citrate. A low aluminum product is produced and stored in low aluminum containing glass.

US 5118794 discloses that viral inactivation in albumin may be performed by terminal heat treatment.

The addition of the terminal step of treating the albumin to inactivate viruses by heating to the method as disclosed by the primary references of US 5561115 or US 5372997 would have been obvious when the primary

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references were taken with the method shown by US 5118794 which demonstrates terminal pasteurization of albumin.

*Response to Arguments*

Applicants' arguments regarding the deficiencies of the primary references, '115 or '997, were rebutted above and are not repeated here.

Claims 14-18, 20-31, 33, 34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5229498 [E] in combination with US 5372997 [B].

The references are relied upon as described below.

US 5229498 discloses a method of removing multivalent metal cations, in particular, aluminum from a protein solution by exchange with monovalent metal cations such as sodium or potassium cations by gel or dia-filtration.

Albumin is an exemplified protein. Specifically, 1M sodium chloride is added to the albumin and the resulting albumin solution was diafiltered against 1M NaCl. The concentration of multivalent metal cations is reduced to below 30µg/l (example 1). In example 4, terminal heat treatment is demonstrated. In example I, a Cohn fraction is used. A Cohn fraction is produced by adding EtOH which is known to inactivate viruses.

US 5372997 discloses the use of a low aluminum containing glass to store albumin which has a reduced aluminum content (col. 6).

The substitution of a mono or dicarboxylic acid sodium salt, such as sodium caprylate or sodium tartrate or sodium acetate for the sodium chloride in the method of US 5229498 would have been obvious because '498 teaches a non-limited exchange of monovalent metal cations for multivalent metal cations, in particular the exchange of sodium cation for aluminum cation. It is apparent that sodium caprylate, sodium acetate or sodium tartrate are sodium salts and therefore release a sodium cation in solution. Therefore, sodium tartrate, sodium acetate, etc., may be substituted for the exemplified sodium salt, sodium chloride in accordance with the teachings of '498.

The subsequent storage of the processed albumin in low aluminum-containing glass would have been obvious when the primary reference was



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taken with the disclosure of US 5372997 which shows that albumin solutions which have had the undesired metal cations removed, will not pick up more metal cations if stored in a low metal-containing container.

*Response to Arguments*

Applicants argue that the examiner does not address the fact that '498 concerns only the exchange of multivalent metal cations with monovalent cations and the reference does not teach the exchange of citrate with the organic molecules recited in the claims.

Please note that the disclosed method starts with a protein, exemplified is human albumin from Cohn's fraction V, see examples, which is contaminated with a multivalent cation such as aluminum ion. Cohn's fraction V is considered to inherently have citrate contamination because it is derived from citrated blood, according to the well known Cohn's fractionation method. While the examiner may not recreate applicants' invention, please note that the claims encompass use of sodium salts of mono or dicarboxylic acids. '498 generically teaches use of the non-limiting genus of sodium cations from any source. Whether one obtains this cation from NaCl or from Na acetate, or Na caprylate is not particularly relevant in the absence of evidence to the contrary. Although removal of citrate is not taught by the reference, a citrate-free product is not required by the claims. The product produced by the process of '498 is low in multivalent metal cations as is the product of the claims.

One of skill in the art would have been motivated at the time of invention to make these substitutions in order to obtain the results as suggested by the references with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

*Conclusion*

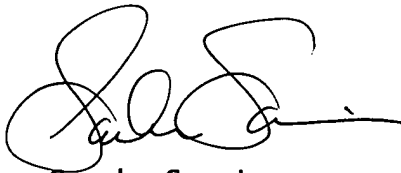
All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1651. The supervisor for 1651 is M. Wityshyn, (703) 308-4743. The normal work schedule for Examiner Saucier is 8:30AM to 6:00PM Tuesday-Friday and every other Monday.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (703) 308-1084. Status inquiries must be directed to the Customer Service Desk at (703) 308-0197 or (703)-308-0198. The number of the Fax Center for the faxing of papers is (703) 308-2742 or (703) 305-3592.

A handwritten signature in black ink, appearing to be 'S. Saucier', with a stylized, cursive script.

Sandra Saucier  
Primary Examiner  
Art Unit 1651  
November 14, 2001